Foot Mouth Disease Virus Affects The Immune Response Of The Host: An Overview

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Abstract
Foot Mouth Disease Virus that spreads among animals with split hooves, such as cows, pigs, and sheep. It causes a disease that makes blisters in the mouth and feet of the animals, and can lead to huge losses for farmers when it breaks out. FMDV belongs to the Picornaviridae family of viruses, and it has a fast life cycle. It can infect and spread through the animals, and make new virus particles in less than seven days. FMDV is a virus that makes animals sick. It can be stopped by the body's defense system, which has different parts. But FMDV has some tricks to avoid the defense system and keep making more viruses, as seen in the lab with mice. One of the virus parts, L pro, stops the cell from making IFN-β, which is a chemical that can fight the virus. This also stops the cell from making its own proteins. Another virus part, 3C pro, breaks a part of the cell that helps make RNA, which is needed for making proteins. FMDV infection causes a temporary decrease in lymphocytes in swine, but the process and the viral protein(s) behind this are unclear. In this review, we have discussed how FMDV interacts with various immune cells such as lymphocytes and antigen presenting cells and what happens as a result.

Keywords, foot and mouth disease, cellular immunity, antibody immunity, T lymphocytes

INTRODUCTI ON

Cloven hoofed livestock are mainly affected by foot and mouth disease (FMD), a very infectious viral disease. (Amir, et al., 2023؛ Ismail, et al., 2023)The FMD virus, which causes the disease, is an Aphthovirus from the Picornaviridae family (Zhang, et al., 2023). The livestock industry suffers serious economic losses from the infection because of its fast spread, high sickness rate, (Aslam, et al.,) and reduced productivity (Yadav, et al., 2020). Some animals that live on farms or in the wild can get sick from a virus. These animals are cows, buffaloes, camels, sheep, goats, and pigs. Many other wild animals can also get sick from the same virus. There are more than 70 kinds of wild animals that can get sick from it (Rahman, et al., 2020). are susceptible to foot and mouth disease. The disease has 7 different serotypes, which are O, A, C, Asia1, SAT1, SAT2, and SAT3, and each of them has its own antigenic and epidemiological subtypes (Li, et al., 2023؛ Njihia, et al., 2022). This diversity is a result of the high mutation rate, recombination, (Ferretti, et al., 2020) and quasi species dynamics of the virus. (Domingo, et al., 2019)

The disease triggers fever and sores on hairless skin areas, such as mouth, tongue, nose, muzzle, teats, and interdigital spaces, which result in less eating and walking difficulties. (Julieth, et al., 2020) The severity of FMD symptoms varies depending on the host species and the viral strain. (Yang, et al., 2022) In cattle and pigs, fever and viremia occur 24 to 48 hours after the virus infects the epithelium. This causes the virus to disseminate to various organs and tissues, and more sores, especially, on the feet and mouth. (Rodríguez-Habibe, et al., 2020) The infection is acute for about 1 week and declines slowly with the growth of a strong immune response.

Except for the countries that are historically disease free (Jamal, et al., 2013),All countries that have animals like cows, sheep, and goats have had foot and mouth disase. The disease is common in many places in Asia, Africa, South America, and Middle East. There are different types of the disease, called O and A, that are found everywhere. Another type, called South African territory, is mostly in Africa (but sometimes in the Middle East). And another type, called Asia1, is only in Asia (Ahmed, et al., 2022). The disease used to come and go with the seasons, but now it stays in some parts of Pakistan all year long, and it can be mild or severe.(Ijaz, et al 2022).

RNA viruses change a lot (10−3 to 10−5 mistakes per letter copied) and make copies of themselves very fast, making many different kinds of viruses, called viral quasispecies (Domingo, et al., 1997). Viral quasispecies can change quickly

to new situations (Domingo, et al.,2021). These different kinds of viruses make RNA viruses very diverse, which helps them cause more diseases and infect more hosts (Braun, et al.,2021).Foot and mouth disease virus, an RNA virus that changes a lot,7 is also used to study how viruses change their host cells and how viral quasispecies change over time (Domingo, et al 2020). The VP1 protein of the FMDV capsid is prone to changes and has important functions in how the virus infects cells, determines its serotype, and interacts with the immune system (Carrillo, et al., 2011). This review examines the available data on how cattle and pigs respond to FMDV infection through cellular and humoral immunity, and how the virus escapes these responses to ensure its survival.

FMDV-induced cell-mediated immunity in cattle and pigs

The immune system reacts to FMDV by stimulating lymphocytes and producing antibodies that neutralize the virus based on its serotype (Rodríguez-Habibe, et al., 2020). The innate immune system has cellular components such as NK cells, DCs, γδ T cells, B cells, macrophages, and granulocytes (Okeke, et al., 2019). These cells are assumed to develop in a similar way as shown in the mouse, which is the most widely used animal model for studying immunity. (Rodríguez et al 2020).

The Natural killer cells

NK cells are a type of cell that helps fight viruses by killing cells that have viruses and making chemicals that stop viruses, such as IFN-γ. (Diaz-Salazar, et al 2020) In big animals like cows, NK cells are in many parts of the body such as spleen, lungs, lymph nodes, liver, blood, and bone marrow. They have CD335 parts that help them kill cells with viruses and make IFN-γ, and they have a CD335+/CD2+/−/CD8+/−/CD3− sign on their outside (Toka, et al., 2013). NK cells from cows with FMDV infection can kill cow cells very well in the lab (Rodríguez-Habibe, et al., 2020). NK cells in pigs are like NK cells in other animals, and they have a CD2+/CD8+/CD3− sign on their outside. (Toka, et al 2009) NK cells can kill FMDV-infected cells better when they get chemicals such as IL-2, IL-12, IL-15, IL-18, or IFN-α. (Toka, et al,.2013) But NK cells in pigs are not good at killing FMDV-infected cells when they do not get these chemicals. They also do not make IFN-γ and do not kill cells that are easy to kill by NK cells, such as FMDV-infected pig cells and K562 cells, when they have FMDV infection. This means that NK cells are not helpful in the first part of FMDV infection in pigs (Toka, et al., 2019). NK cells are stopped by MHC-I proteins on the cell outside; when MHC-I proteins are less, NK cells are more active during FMDV infection. (Medina, et al., 2018) NK cells can kill infected cells by making chemicals such as IFN-γ and TNF-α, and by using granzyme, perforin, and Fas ligand. (Konjević, et al., 2019). NK cells also help control the immune system by making DCs work better. The way NK cells and DCs work together changes how T cells work, which makes NK cells important for the immune system that learns from infections. (Kucuksezer, et al., 2021).

The Gamma/Delta Cells

The number of γδ T cells in the dome part of the Peyer's patches changes before and after birth in cows: it goes up at first, but goes down after birth. But the number of γδ T cells in the intestinal villi is low before birth, but goes up after birth. (David, et al., 2003) In sheep, the thymus controls the normal γδ T cell types in the outside parts of the body, and it has to work all the time in the animal's life. (Sinkora, et al., 2016) In pigs, the γδ T cells are easier: they have 12 different mixes that are in 2 big groups: (1) CD4, γδ T cells that are split by CD2/CD8 αα parts, and (2) CD4+, γδ T cells that have CD1, CD2, and CD8 αα, but do not go to the outside parts of the body.

Young ruminants and swine have 20% to 50% of their T cells with γδ TCR. These cells recognize antigens without MHC, but their specific antigens are unknown. Their role in viral immunity is unclear. The γδ T cells act like innate immune cells by killing infected cells without MHC and making inflammatory cytokines. (Baldwin, et al., 2021)

Some reports say that γδ T cells help cuts heal by making insulin-like growth thing. Most of the information on how FMD virus changes host protection comes from pigs. When animals got a lot of FMD vaccine, the pig γδ T cells made mRNA of different chemicals that stop viruses and call other cells, which means they have a role in natural protection to infection or vaccination. These cells were also from FMDV-vaccinated cows and they showed that they could stop and kill infected cells.30 Some studies also showed that cow γδ T cells could work as APCs because they have MHC class II and CD 13 and can take and break foreign proteins. (Rodríguez et al 2020) But it is not clear if this working is caused by direct touch of γδ T cells with virus or something else.

Cells of the dendritic system

Dendritic cells (DCs) scan for antigens, including vaccine antigen, in the margins and direct them to T cell-rich areas of lymph nodes to trigger immune responses. Antigen-presenting cells (APCs) mature and take up more antigen, presenting viral peptides through MHC classes I and II molecules (Male, et al., 2020). These peptides on macrophages stimulate and sustain T cell response against FMD virus (Rodríguez-Habibe, et al.,2020). A subset of DCs in cattle, called plasmacytoid (pDCs), can produce type I IFN, which is crucial for controlling viral infections, especially those that block type I IFN signaling. In blood, lymph nodes, and pseudo afferent lymph, these cells are very few. A group of pDCs with specific signs (NK−, TCR−, MHC II+, CD3−, CD4+, CD11c−, CD14−, CD21−, CD45RB+, CD172a+, and CD32+) was found. They make a lot of type I IFN when they get TLR9 agonist CpG and FMDV immune complexes (Reid, et al., 2011). But they did not work with UV-inactivated FMDV or FMDV empty capsids. Making CD4 cells less in vivo made type I IFN less in the blood of cows with FMDV infection. This shows that pDCs are important for protection in vaccinated animals, as type I IFN needs virus antibody complexes in vivo (Ali, et al., 2019). DCs that make a lot of type I IFN were also in mesenteric lymph nodes, showing their role in lymph nodes (Medina, et al., 2018).

The role of type I IFN is not clear in the first parts of infection, as making type I IFN–making CD4+ cells less did not change the disease. Also, DCs from monocytes (MoDCs) were linked with dead virus–made FMDV-specific CD4+ memory T lymphocytes, saying that these complexes could be used in making FMDV vaccine (McNab, et al., 2015).

IFN type III in bovines

The first cell reaction to a virus infection makes antiviral chemicals, including type I IFN-α/IFN-β. A new family of IFNs, type III IFN-π, has been found in different animals, such as humans, pigs, chickens, and mice. Also, a type III IFN in cows (boIFN-3π3) has been found, studied, and made. After infection with viruses or bacteria inside cells, IFN-π–like IFN-α/IFN-β is made fast in a cell (Kabát, et al., 2013). Type III IFN, compared to type I IFN, makes similar natural antiviral reactions but uses different parts for signaling. The working of IFN happens through a two-part cell part made of IL-10Rβ, shared by the IL-10 family of chemicals, and IL-28Rα (Tagawa, et al., 2011). when IFN touches its part, it makes the Janus kinase-signal transducer and transcription activator work, which starts a signal change that leads to the making of IFN-stimulated genes (Stanifer, et al., 2019). The main working of IFN-π and all other IFNs is to stop virus making in infected cells and stop the virus from going to not infected cells. In places where foot-and-mouth disease (FMD) is common, disease control mostly uses vaccination with dead virus vaccines with adjuvants.

But the use of FMDV vaccines may have some problems. To solve these problems, a different vaccine has been made, in which not working human adenovirus type 5 (Ad5) was used to give empty FMDV capsids (Mignaqui, et al., 2019). Research has shown that pigs treated with Ad5s, making pig type I IFN (Ad5-poIFN-α/β), got full protection from FMDV infection one day after injection, and this protection lasted for 3 to 5 days (Medina, et al., 2018).

But in cows, a similar way only made a 1 to 2-day wait in the disease, with less bad signs (Perez-Martin, et al., 2012). New research has shown that boIFN-3 stopped virus making against vesicular stomatitis virus and FMDV in cow cell culture. Also, it was shown that treating cows with Ad5-boIFN-3 made wide antiviral working with more making of IFN-stimulated genes in different parts, including those in the skin and upper breathing tract (Medina, et al., 2020).

Innate immunity to FMDV is mediated by Toll-like receptors

Innate immune cells function according to the receptors on their surfaces (Kucuksezer, et al., 2020). Pathogen recognition receptors (PRRs), known as toll-like receptors (TLRs) collectively, are found in NK cells, dendritic cells (DCs), and γδ T cells. These receptors identify pathogen-associated molecular patterns present on pathogens' surfaces. Understanding these signaling molecules is crucial for creating potent preparations for vaccines or immunotherapeutics. When pathogens are around, PRRs like TLRs are adjusted, boosting immunity against viruses (Carty, et al., 2021).

When FMDV infects animals, it makes a protein called TLR4 more active in their nose tissues (Zhang et al.). This also makes more mRNA for type I IFNs, which are molecules that fight viruses. This was surprising because FMDV is an RNA virus, and usually RNA viruses make TLR3 more active, not TLR4. TLR3 can sense dsRNA, which is a kind of RNA that many RNA viruses make when they copy themselves. TLR4 usually reacts to lipopolysaccharides, which are molecules from some bacteria (Mazgaeen et al., 2020).Some immune cells called NK cells have TLR7 and TLR8 on them. These are proteins that can sense some viruses. When TLR7 and TLR8 are activated, NK cells can kill infected cells better. But they need help from other immune cells called DCs. If DCs are removed, NK cells cannot kill as well (Wculek, et al., 2020). Other studies have shown that some DCs have TLR4, TLR5, TLR7, and TLR9 on them. In pigs, these TLRs can make IFN when they sense CpG, which is a molecule that some viruses have. IFN can help fight viruses (Facci, et al., 2013). Some researchers have found that FMDV has RNA molecules that can activate TLR7 in pigs. This makes IFN and T helper 1 cytokines, which are molecules that help the immune system. This means that we might be able to use these TLRs to make the immune system stronger against viral diseases (Meng, et al., 2020).In more research, some DCs were found to have TLR4, TLR5, TLR7, and TLR9 on them. In pigs, these TLRs made IFN when they sensed CpG (Facci, et al., 2013).In other research, some DCs were found to have TLR4, TLR5, TLR7, and TLR9 on them. In pigs, these TLRs made IFN when they sensed CpG (Facci, et al., 2013). Some researchers have found that FMDV has RNA molecules that can activate TLR7 in pigs. This makes IFN and T helper 1 cytokines. This means that we might be able to use these TLRs to make the immune system stronger against viral diseases (Meng, et al., 2020).

There are other proteins that can sense viruses in immune cells. They are called RIG-I–like receptors (RLRs) (Wicherska-Pawłowska, et al., 2021). TLRs are on the outside or inside of the cell, but RLRs are in the cell fluid. This makes them better at finding viral RNA. For example, a protein called MDA5 can find FMDV in pig kidney cells. Another virus called classical swine fever virus can be found by MDA5, TLR3, and RIG-I. These proteins can make IFN-β, which is another molecule that fights viruses (Kim, et al., 2021). Ma, et al. showed that FMDV has a protein called L pro that can stop type I IFNs from being made. It does this by stopping RIG-I from working properly. This supports the idea that FMDV mainly uses MDA5 to signal.

Immune response at the cellular level

To find out how cattle fight FMDV, researchers used to look for antibodies in their nose and throat fluids. These antibodies are proteins that can stop the virus. Cattle that get FMDV make more antibodies in their blood after 7 to 10 days. These antibodies are very specific to the type of FMDV. The antibody level goes up after 28 days and stays high. In some cattle, this antibody response lasts for up to 40 weeks (Pega et al., 2015).

Li et al. in 2010 showed that cattle get better from FMDV when they have neutralizing antibodies. These are antibodies that can block the virus from infecting cells. Pega et al. (2013) found these antibodies in the nose and saliva of cattle that got FMDV through their nose. McVicar and Sutmoller also found these antibodies in the saliva and throat fluids of cattle that got FMDV the same way. This suggests that the antibody response in the nose and throat might be different from the one in the blood. Other studies found FMDV-specific IgM and IgA in the throat fluids a week after infection. These antibodies might come from the blood (Gordon et al., 2022). Only IgA antibodies found later in the infection were related to the nose and throat response. But there is no evidence of a nose and throat response before day 7 (Pega et al., 2013).

FMDV can change a lot because it has different parts that the antibodies can recognize. This means that the antibodies might only work against one type of FMDV, not others. Studies have shown that animals that get infected with one type of FMDV can still get infected with six other types. This makes it hard to diagnose FMDV by looking at the antibodies (Yang et al., 2016). Yang et al. made two FMDV antibodies (mAbs) from mice that got FMDV type O (whole virus, 140S) or FMDV type A (part of the virus, 12S). These mAbs (F1412SA and F21140SO) could recognize all seven types of FMDV in a test called ELISA. This means that they can bind to parts of the virus that are the same in all types. Both mAbs are IgG1 and have kappa light chains.

Pega et al. saw that cattle that got FMDV through the air made more antibody-producing cells (ASC) in their immune organs. They saw that FMDV-ASC appeared in all the cattle at day 4 after infection. The most active organs were the ones near the lungs and the main antibody type was IgM, followed by IgG1. The number of FMDV-ASC went up at day 5 and 6, especially in the upper airway organs. The antibody response in the nose and throat was weaker than the one in the blood. The high level of IgM in the blood at day 5 matched with a low level of viral RNA in the blood. This means that cattle make a fast and strong antibody response in their airways after getting FMDV through the nose. The types and timing of the antibodies show that they do not need T cells to help them. They can clear the virus with IgM in cattle that get FMDV from the same type (Pega et al., 2013).

FMDV's strategies for evading the immune response

FMDV is a virus that makes mammal cells less able to fight infections. It does this by stopping some molecules that can stop the virus and by hiding some proteins that show the virus is there. It also affects how the cells make and send other proteins (Sarry et al., 2022). Medina et al. in 2018 showed that the virus makes the cells' first defense weaker in the lab and also touches some cells that can show the virus to other cells. This touch between the cells and the virus makes the cells' defense worse, and it takes longer for some cells called T cells to start fighting the virus. This helps the virus make more copies of itself.

Impact of FMDV on active immunity Interruption

FMDV starts by infecting the cells that cover the body. The virus sticks to a part of the cell and then goes inside the cell (Martin-Acebes et al., 2009). The virus has RNA that tells the cell how to make the virus parts. Some of these parts are for the outside of the virus (capsid proteins) and some are for the inside (NS proteins). The NS proteins help the virus use the cell to make more viruses and stop the cell from fighting back. Some FMDV parts in the cell have special jobs, like stopping the first defense (Toka et al., 2013).

One of the FMDV parts is a proteinase called L pro. It cuts itself from the long virus part (Mann et al., 2019). It also cuts a part of the cell called eIF4G, which helps the cell make proteins from mRNA. This stops the cell from making its own proteins, but the virus can still make its proteins (López-Lastra et al., 2010). L pro also stops the cell from making Type I interferon (IFN), which is a molecule that can fight the virus. It does this by stopping IFN-β from being made and sent (Khabar et al., 2007). Studies in the lab show that FMDV infection, with L pro, breaks down a part of the cell called NF-κB, which helps make IFN and other things for the first defense (De et al., 2007). We don't know exactly how L pro does this, but we know that it needs to stay in the cell and go to the center of the cell. If we change a part of L pro that helps it stay in the cell, the virus becomes weaker in the lab and in animals (Golde et al., 2011). L pro also breaks down some parts of the cell called IFN regulatory factor 3/7 in the lab, which might make it harder for the cell to fight the virus, but we don't know if this happens during FMDV infection. Some cells called cytotoxic T lymphocytes (CTLs) can find and kill cells that have the virus. They do this by seeing some virus parts on the cell surface (Nutt et al., 2019). We have seen CTLs fight FMDV (Diaz-San et al., 2017). But FMDV has ways to avoid this. The NS proteins 2B and 2C, or their part 2BC, stop the cell from sending proteins, as shown in the lab (Fullen et al., 2011). Cells that have FMDV have less MHC class I molecules on their surface. These are molecules that show the virus parts to the CTLs. This is a trick that some cancers and viruses use to escape from the CTLs (Golde et al., 2011). But the cell's defense has another way to survive. It sends some cells called natural killer (NK) cells to kill cells that have low MHC class I. However, during FMDV infection, NK cells are not very good at killing cells or making IFN-γ, which is a molecule that helps the defense (Toka et al., 2013). There are other FMDV NS proteins that make the virus stronger, but we don't know how they work. FMDV is a virus that makes animals sick. It has some parts that make it stronger and harder to stop, but we don't know how they work. For example, Falk et al. saw that one part of the virus called 3Cpro cuts some parts of the cell that make RNA, which is needed for making proteins. 3Cpro also cuts some parts of the cell that help with translation, which is the process of making proteins from RNA (Dougherty et al., 2010).

FMDV Interaction with DCs

FMDV also affects some cells that can show the virus to other cells. These cells are important for the immune system, which is the body's defense against infections. When FMDV gets into the body, it first infects the cells that cover the body. Then it meets the cells that can show the virus. This makes the body tissues hurt, and the body makes some chemicals that start the immune system. These chemicals make the blood vessels bigger and leaky, and bring some white blood cells to the infection site (Chrousos et al., 2000). These white blood cells can change into different types of cells that can show the virus (Kou et al., 2011).

In the lab, FMDV makes the cells that can show the virus less able to do their job. It lowers some molecules on their surface that help them talk to T cells, which are cells that can fight the virus. When the cells that can show the virus are exposed to live FMDV, they make more IL-10, which is a chemical that can weaken the immune system, in T cells that are with them (Guzman et al., 2014). Also, when the cells that can show the virus are with some other cells called splenocytes, live FMDV makes them have more IgM, which is a type of antibody that can stop the virus. This IgM makes the cells that can show the virus make more IL-6, which then makes the splenocytes make more IL-10, this time from B cells, which are cells that can make antibodies (Puga et al., 2012). Some cells that can show the virus come from other cells called monocytes. These cells can change into cells that can show the virus when there is inflammation, like in FMDV infection. These cells are interesting for researchers. Some of these cells, like some cells from pig skin, can make IFN-α, which is a chemical that can fight the virus, when they are exposed to different types of FMDV in the lab. But when pigs get FMDV, their monocytes cannot change into cells that can show the virus in the lab, and they cannot make IFN-α when they meet some molecules that can start the immune system (Golde et al., 2011). However, monocytes from FMDV-infected pigs can still become cells that can show the virus by keeping some molecules on their surface and breaking down the virus. These cells cannot make the T cells react, which means they are not working well. FMDV might stop IFN responses by turning off some genes that are important for the cells that can show the virus (Díaz-San Segundo et al., 2009).

There is another type of cells that can show the virus called plasmacytoid DCs (pDCs). They are different from other cells and they can make a lot of IFNs when they meet viruses. Pig pDCs that are infected with FMDV and antibodies can make IFN-α. But they do not get infected or make IFN-α when they meet the virus alone (Rodríguez-Habibe et al., 2020). When pigs get FMDV, they have less pDCs in their blood. The pDCs that are left can still make IFN-α when they meet FMDV or some molecules that can start the immune system, but they lose this ability for a while (Chen et al., 2015).

FMDV-induced early antibody response

FMDV is a virus that makes animals sick. When cattle get FMDV, they make antibodies that can stop the virus. Antibodies are proteins that fight infections. They can measure antibodies in the blood as IgM, IgA, and IgG. IgM shows up first, after 3 to 4 days. Then IgA and IgG show up later, after 1 to 2 weeks (Eschbaumer et al., 2016). Pigs have a similar response to FMDV (Senthilkumaran et al., 2017). In cattle, the IgG antibodies become stronger even without help from T cells, which are cells that can fight the virus. The cattle can make IgM antibodies without T cell help, too, and they have a lot of IgM in their blood even with T cell help (Habiela et al., 2017). These antibody responses may start without help from dendritic cells (DCs), which are cells that can show the virus to other cells. But they may need some things from DCs, like BAFF, to change the type of antibodies they make. In a lab model with pig cells, they saw that both IL-2 and BAFF were needed for memory IgG responses, which are antibodies that remember the virus. This shows the effect of T cell help using BAFF from DCs and IL-2 from outside (Woolsey et al., 2018). DCs may make IL-2 sometimes, but we don't know for sure how they help the first antibody response to FMDV. We think that DCs help T cells respond better, which will make memory B cells after vaccination. This will protect the animals from FMDV (McCullough et al., 2019).

T cell Response Manipulation by FMDV

When pigs get FMDV, their T cell function gets worse (Zhu et al., 2022). In sick animals, they have fewer lymphocytes, which are white blood cells, especially CD8+ cells, which are a type of T cells. This starts around day 2 after infection and gets better by day 4. But even then, the T cells don't react well to concanavalin A, which is something that makes them grow. This means that they are still not working well (Golde et al., 2011). Another study showed that FMDV type C infected both T and B cells a lot (30% and 60%, respectively). This made them have fewer lymphocytes, especially CD8+ T cells, and they also didn't react well to concanavalin A (Ostrycharz et al., 2022). The lymphocyte infection didn't kill the cells, so that was not the reason for having fewer lymphocytes. They thought that maybe IFN made the lymphocytes move from the blood to the tissues and the infection site. IFN is a chemical that can fight the virus. Studies with mice supported this idea, showing that giving IFN-α to mice made them have fewer lymphocytes, but not in mice that didn't have the IFN-α/IFN-β receptor. This is similar to what they saw in sick pig blood, which had a lot of type I IFNs (Rosell et al., 2018; Cai et al., 2017). This kind of IFN-induced lymphopenia, which means having fewer lymphocytes, may not mean that the immune system is weaker, but it may help the animals (Kamphuis et al., 2006).

In sick pigs, having more lymphocytes again seems to be related to different movements because of cytokine signals, rather than just losing and making more lymphocytes (Toka et al., 2009). Cytokines are chemicals that help the immune system. They also saw that FMDV infected cow lymphocytes in the lab, but they didn't react much to concanavalin A (Oh et al., 2012). But T cells from sick cows grew well when they met other things that were not FMDV or concanavalin A during FMDV infection (Golde et al., 2011). They also saw a small T cell response to FMDV antigen, which is a part of the virus, with low levels of IL-10 in the blood using tests that measured growth until day 19 after infection (Golde et al., 2011). FMDV is a virus that makes animals sick. It is hard to know how it affects T cells, which are cells that can fight the virus. This is because different things happen in the lab and in the animals with different types of FMDV, especially

in cows and pigs. Also, things might change if the virus is grown in cells that cannot make the part that the virus sticks to, or if the virus is taken from animals (Shin et al., 2013). To solve this problem, we need to do studies that compare the virus type and how it looks with how T cells respond to FMDV infection, both in the lab and in the animals (Domingo et al., 2020).

CONCLUSION

Many studies show that antibodies are more important than the first defense in the early response to FMDV infection. Antibodies are proteins that can stop the virus. In pigs, FMDV makes more copies of itself very fast and makes a lot of virus in the blood. This lowers the level of IFN, which is a chemical that can fight the virus. This makes the pigs have fewer lymphocytes, which are white blood cells, and makes the first defense weaker. In cows, FMDV does not lower the IFN level as much as in pigs. They also do not have fewer lymphocytes or a weaker defense. It is important to know how FMDV infects animals to control the disease better. We need to know how different parts of the immune system, which is the body's defense against infections, affect how the disease gets worse and hurts the animals. This will help us learn more about how the virus spreads and how to stop it

REFERENCES

1. Ahmed, W. A. K. (2022). *Epidemiological Studies of Foot-and-Mouth Disease in Northern and Southern Darfur States, Western Sudan* (Doctoral dissertation, Sudan University of Science & Technology).
2. Ali, S., Mann-Nüttel, R., Schulze, A., Richter, L., Alferink, J., & Scheu, S. (2019). Sources of type I interferons in infectious immunity: plasmacytoid dendritic cells not always in the driver's seat. *Frontiers in immunology*, *10*, 778.
3. Amir, A., Qadeer, I., Munir, S., Ayoub, K., & Kalsoom, H. (2023). Diagnosis and Vaccination of Animals that are Affected by Foot and Mouth Disease. *Journal of Zoology and Systematics*, *1*(2), 58-68.
4. Aslam, M., & Alkheraije, K. A. (2023). The prevalence of foot-and-mouth disease in Asia. *Frontiers in Veterinary Science*, *10*.
5. Baldwin, C. L., Damani-Yokota, P., Yirsaw, A., Loonie, K., Teixeira, A. F., & Gillespie, A. (2021). Special features of γδ T cells in ruminants. *Molecular Immunology*, *134*, 161-169.
6. Braun, K. M. (2021). *Embracing Randomness: Within-and Between-Host Evolution of Two RNA Viruses* (Master's thesis, The University of Wisconsin-Madison).
7. Cai, B., Bai, Q., Chi, X., Goraya, M. U., Wang, L., Wang, S., & Chen, J. L. (2017). Infection with classical swine fever virus induces expression of type III interferons and activates innate immune signaling. *Frontiers in microbiology*, *8*, 2558.
8. Carrillo, C. (2011). Microbial forensics of RNA viruses: Foot-and-mouth disease virus. In B. Budowle, S. E. Schutzer, R. G. Breeze, P. S. Keim, & S. A. Morse (Eds.), *Microbial Forensics* (pp. 75-87). Academic Press.
9. Carty, M., Guy, C., & Bowie, A. G. (2021). Detection of viral infections by innate immunity. *Biochemical pharmacology*, *183*, 114316.
10. Chen, W. Y. (2015). *Studies on the interaction between porcine reproductive and respiratory syndrome virus and its natural host cell* (Doctoral dissertation, University of Illinois at Urbana-Champaign).
11. Chrousos, G. P. (2000). Stress, chronic inflammation, and emotional and physical well-being: concurrent effects and chronic sequelae. *Journal of Allergy and Clinical Immunology*, *106*(5), S275-S291.
12. David, C. W., Norrman, J., Hammon, H. M., Davis, W. C., & Blum, J. W. (2003). Cell proliferation, apoptosis, and B-and T-lymphocytes in Peyer's patches of the ileum, in thymus and in lymph nodes of preterm calves, and in full-term calves at birth and on day 5 of life. *Journal of dairy science*, *86*(10), 3321-3329.
13. De Los Santos, T., Diaz-San Segundo, F., & Grubman, M. J. (2007). Degradation of nuclear factor kappa B during foot-and-mouth disease virus infection. *Journal of virology*, *81*(23), 12803-12815.
14. Diaz-Salazar, C., & Sun, J. C. (2020). Natural killer cell responses to emerging viruses of zoonotic origin. *Current opinion in virology*, *44*, 97-111.
15. Diaz-San Segundo, F., Medina, G. N., Stenfeldt, C., Arzt, J., & de Los Santos, T. (2017). Foot-and-mouth disease vaccines. *Veterinary microbiology*, *206*, 102-112.
16. Díaz-San Segundo, F., Rodríguez-Calvo, T., de Avila, A., & Sevilla, N. (2009). Immunosuppression during acute infection with foot-and-mouth disease virus in swine is mediated by IL-10. *PLoS One*, *4*(5), e5659.
17. Domingo, E. (2020). Long-term virus evolution in nature. In E. Domingo (Ed.), *Virus as Populations* (pp. 225-246). Academic Press.
18. Domingo, E. (2020). Virus population dynamics examined with experimental model systems. In E. Domingo (Ed.), *Virus as Populations* (pp. 195-224). Academic Press.
19. Domingo, E. J. J. H., & Holland, J. J. (1997). RNA virus mutations and fitness for survival. *Annual review of microbiology*, *51*(1), 151-178.
20. Domingo, E., Ruiz-Jarabo, C. M., Arias, A., García-Arriaza, J., & Escarmís, C. (2019). Quasispecies dynamics and evolution of foot-and-mouth disease virus. In F. Sobrino & E. Domingo (Eds.), *Foot and Mouth Disease* (pp. 261-304). CRC Press.
21. Domingo, E., Soria, M. E., Gallego, I., de Ávila, A. I., García-Crespo, C., Martínez-González, B., & Perales, C. (2020). A new implication of quasispecies dynamics: Broad virus diversification in absence of external perturbations. *Infection, Genetics and Evolution*, *82*, 104278.

22. Dougherty, J. D., Park, N., Gustin, K. E., & Lloyd, R. E. (2010). Interference with cellular gene expression. *The picornaviruses*, 163-180.
23. Eschbaumer, M., Stenfeldt, C., Rekant, S. I., Pacheco, J. M., Hartwig, E. J., Smoliga, G. R., ... & Arzt, J. (2016). Systemic immune response and virus persistence after foot-and-mouth disease virus infection of naive cattle and cattle vaccinated with a homologous adenovirus-vectored vaccine. *BMC veterinary research*, *12*(1), 1-18.
24. Facci, M. (2013). *The immunomodulation of porcine immune cells by innate and synthetic host defense peptides* (Doctoral dissertation, University of Saskatchewan).
25. Ferretti, L., Pérez-Martín, E., Zhang, F., Maree, F., de Klerk-Lorist, L. M., van Schalkwykc, L & Ribeca, P. (2020). Pervasive within-host recombination and epistasis as major determinants of the molecular evolution of the foot-and-mouth disease virus capsid. *PLoS Pathogens*, *16*(1), e1008235.
26. Fullen, D. J. (2011). The effects of foot and mouth disease virus 2BC protein upon the secretory pathway. University of Surrey (United Kingdom).
27. Golde, W. T., de Los Santos, T., Robinson, L., Grubman, M. J., Sevilla, N., Summerfield, A., & Charleston, B. (2011). Evidence of activation and suppression during the early immune response to foot-and-mouth disease virus. *Transboundary and emerging diseases*, *58*(4), 283-290.
28. Gordon, L. (2022). Investigating the role of persisting antigen in immunity against foot-and-mouth disease virus.
29. Guzman, E., Hope, J., Taylor, G., Smith, A. L., Cubillos-Zapata, C., & Charleston, B. (2014). Bovine γδ T cells are a major regulatory T cell subset. *The Journal of Immunology*, *193*(1), 208-222.
30. Habiela, M. (2017). The Role of Follicular Dendritic Cells and Persisting Foot-And-Mouth Disease Virus Antigens as Determinants of Immune Responses to the Virus (Doctoral dissertation, University of Cambridge (United Kingdom).
31. Ijaz, M., Ali, M. M., Awan, F., Ishaq, M., & Ahmad, A. (2022). FMD virus spillover from domestic livestock caused outbreak in captive wild ungulates: First report from Pakistan. *Acta Tropica*, *231*, 106439.
32. Ismail, I., Indarjulianto, S., Yusuf, S., & Purba, F. Y. (2023, May). Clinical Examination of Foot and Mouth Disease of Dairy Cows in Sukamurni, Cilawu, Garut, West Java, Indonesia. In *IOP Conference Series: Earth and Environmental Science* (Vol. 1174, No. 1, p. 012005). IOP Publishing.
33. Jamal, S. M., & Belsham, G. J. (2013). Foot-and-mouth disease: past, present and future. *Veterinary research*, *44*, 1-14.
34. Julieth, E. V. A. N. C. E. (2020). *Molecular detection and evolutionary characteristics of recently recovered serotypes a and o foot-and-mouth disease viruses in selected areas of Tanzania* (Doctoral dissertation, Sokoine University of Agriculture).
35. KABÁT, P. (2013). Interferons lambda, new cytokines with antiviral activity. *Acta virologica*, *57*, 171-179
36. Khabar, K. S., & Young, H. A. (2007). Post-transcriptional control of the interferon system. *Biochimie*, *89*(6-7), 761-769.
37. Kim, H., Kim, A. Y., Choi, J., Park, S. Y., Park, S. H., Kim, J. S., ... & Ko, Y. J. (2021). Foot-and-mouth disease virus evades innate immune response by 3C-targeting of MDA5. *Cells*, *10*(2), 271.
38. Konjević, G. M., Vuletić, A. M., Martinović, K. M. M., Larsen, A. K., & Jurišić, V. B. (2019). The role of cytokines in the regulation of NK cells in the tumor environment. *Cytokine*, *117*, 30-40.
39. Kou, P. M., & Babensee, J. E. (2011). Macrophage and dendritic cell phenotypic diversity in the context of biomaterials. *Journal of biomedical materials research Part A*, *96*(1), 239-260.
40. Kucuksezer, U. C., Aktas Cetin, E., Esen, F., Tahrali, I., Akdeniz, N., Gelmez, M. Y., & Deniz, G. (2021). The role of natural killer cells in autoimmune diseases. *Frontiers in immunology*, *12*, 622306.
41. Li, L. J. (2010). Review of hand, foot and mouth disease. *Frontiers of Medicine in China*, *4*, 139-146.
42. Li, Q., Wubshet, A. K., Wang, Y., Heath, L., & Zhang, J. (2023). B and T Cell Epitopes of the Incursionary Foot-and-Mouth Disease Virus Serotype SAT2 for Vaccine Development. *Viruses*, *15*(3), 797.
43. López-Lastra, M., Ramdohr, P., Letelier, A., Vallejos, M., Vera-Otarola, J., & Valiente-Echeverría, F. (2010). Translation initiation of viral mRNAs. *Reviews in medical virology*, *20*(3), 177-195.
44. Ma, X. X., Ma, L. N., Chang, Q. Y., Ma, P., Li, L. J., Wang, Y. Y., ... & Cao, X. (2018). Type I interferon induced and antagonized by foot-and-mouth disease virus. *Frontiers in microbiology*, *9*, 1862.
45. Male, D., Male, V., & Peebles, R. S. (2020). *Immunology E-Book*. Elsevier Health Sciences.
46. Mann, K. S., & Sanfaçon, H. (2019). Expanding repertoire of plant positive-strand RNA virus proteases. *Viruses*, *11*(1), 66.
47. Martin-Acebes, M. A., Gonzalez-Magaldi, M., Vazquez-Calvo, A., Armas-Portela, R., & Sobrino, F. (2009). Internalization of swine vesicular disease virus into cultured cells: a comparative study with foot-and-mouth disease virus. *Journal of virology*, *83*(9), 4216-4226.
48. Mazgaeen, L., & Gurung, P. (2020). Recent advances in lipopolysaccharide recognition systems. *International journal of molecular sciences*, *21*(2), 379.
49. McCullough, K. C., & Sobrino, F. (2019). Immunology of foot-and-mouth disease. In *Foot and Mouth Disease* (pp. 175-222). CRC Press.
50. McNab, F., Mayer-Barber, K., Sher, A., Wack, A., & O'garra, A. (2015). Type I interferons in infectious disease. *Nature Reviews Immunology*, *15*(2), 87-103.
51. Medina, G. N., De Los Santos, T., & Diaz-San Segundo, F. (2020). Use of IFN-based biotherapeutics to harness the host against foot-and-mouth disease. *Frontiers in Veterinary Science*, *7*, 465.

52. Meng, Z., Chen, Y., & Lu, M. (2020). Advances in targeting the innate and adaptive immune systems to cure chronic hepatitis B virus infection. *Frontiers in Immunology*, *10*, 3127.
53. Mignaqui, A. C., Ruiz, V., Durocher, Y., & Wigdorovitz, A. (2019). Advances in novel vaccines for foot and mouth disease: focus on recombinant empty capsids. *Critical reviews in biotechnology*, *39*(3), 306-320.
54. Nguyen, H. T. T., Guevarra, R. B., Magez, S., & Radwanska, M. (2021). Single-cell transcriptome profiling and the use of AID deficient mice reveal that B cell activation combined with antibody class switch recombination and somatic hypermutation do not benefit the control of experimental trypanosomosis. *PLoS pathogens*, *17*(11), e1010026.
55. Njihia, L. W. (2022). *Molecular Characterization of Circulating Foot and Mouth Disease Virusserotypes a, Sat1 and Sat2 in Kenya From 2019 to 2020 in Relation to the Vaccine* (Doctoral dissertation, University of Nairobi).
56. Nutt, S. L., & Huntington, N. D. (2019). Cytotoxic T lymphocytes and natural killer cells. In *Clinical Immunology* (pp. 247-259). Elsevier.
57. Oh, Y., Fleming, L., Statham, B., Hamblin, P., Barnett, P., Paton, D. J., ... & Parida, S. (2012). Interferon-γ induced by in vitro re-stimulation of CD4+ T-cells correlates with in vivo FMD vaccine induced protection of cattle against disease and persistent infection.
58. Okeke, E. B., & Uzonna, J. E. (2019). The pivotal role of regulatory T cells in the regulation of innate immune cells. *Frontiers in immunology*, *10*, 680.
59. Ostrycharz, E., & Hukowska-Szematowicz, B. (2022). Micro-Players of Great Significance—Host microRNA Signature in Viral Infections in Humans and Animals. *International Journal of Molecular Sciences*, *23*(18), 10536.
60. Pega, J., Bucafusco, D., Di Giacomo, S., Schammas, J. M., Malacari, D., Capozzo, A. V., ... & Perez-Filgueira, M. (2013). Early adaptive immune responses in the respiratory tract of foot-and-mouth disease virus-infected cattle. *Journal of virology*, *87*(5), 2489-2495.
61. Pega, J., Di Giacomo, S., Bucafusco, D., Schammas, J. M., Malacari, D., Barrionuevo, F., ... & Pérez-Filgueira, M. (2015). Systemic foot-and-mouth disease vaccination in cattle promotes specific antibody-secreting cells at the respiratory tract and triggers local anamnestic responses upon aerosol infection. *Journal of virology*, *89*(18), 9581-9590.
62. Perez-Martin, E., Weiss, M., Diaz-San Segundo, F., Pacheco, J. M., Arzt, J., Grubman, M. J., & de los Santos, T. (2012). Bovine type III interferon significantly delays and reduces the severity of foot-and-mouth disease in cattle. *Journal of virology*, *86*(8), 4477-4487.
63. Puga, I., Cols, M., Barra, C. M., He, B., Cassis, L., Gentile, M & Cerutti, A. (2012). B cell–helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. *Nature immunology*, *13*(2), 170-180.
64. Rahman, A. U., Dhama, K., Ali, Q., Raza, M. A., Chaudhry, U., & Shabbir, M. Z. (2020). Foot and mouth disease in a wide range of wild hosts: a potential constraint in disease control efforts worldwide particularly in disease-endemic settings. *Acta Tropica*, *210*, 105567.
65. Reid, E., Juleff, N., Gubbins, S., Prentice, H., Seago, J., & Charleston, B. (2011). Bovine plasmacytoid dendritic cells are the major source of type I interferon in response to foot-and-mouth disease virus in vitro and in vivo. *Journal of virology*, *85*(9), 4297-4308.
66. Rodríguez-Habibe, I., Celis-Giraldo, C., Patarroyo, M. E., Avendaño, C., & Patarroyo, M. A. (2020). A comprehensive review of the immunological response against foot-and-mouth disease virus infection and its evasion mechanisms. *Vaccines*, *8*(4), 764.
67. Roselli, F., Chandrasekar, A., & Morganti-Kossmann, M. C. (2018). Interferons in traumatic brain and spinal cord injury: current evidence for translational application. *Frontiers in neurology*, *9*, 458.
68. Saha, B., Prasanna, S. J., Chandrasekar, B., & Nandi, D. (2010). Gene modulation and immunoregulatory roles of Interferonγ. *Cytokine*, *50*(1), 1-14..
69. Sarry, M., Vitour, D., Zientara, S., Bakkali Kassimi, L., & Blaise-Boisseau, S. (2022). Foot-and-mouth disease virus: molecular interplays with IFN response and the importance of the model. *Viruses*, *14*(10), 2129.
70. Senthilkumaran, C., Yang, M., Bittner, H., Ambagala, A., Lung, O., Zimmerman, J., ... & Nfon, C. (2017). Detection of genome, antigen, and antibodies in oral fluids from pigs infected with foot-and-mouth disease virus. *Canadian Journal of Veterinary Research*, *81*(2), 82-90.
71. Shin, H., & Iwasaki, A. (2013). Tissue-resident memory T cells. *Immunological reviews*, *255*(1), 165-181.
72. Sinkora, M., & Butler, J. E. (2016). Progress in the use of swine in developmental immunology of B and T lymphocytes. *Developmental & Comparative Immunology*, *58*, 1-17.
73. Stanifer, M. L., Pervolaraki, K., & Boulant, S. (2019). Differential regulation of type I and type III interferon signaling. *International journal of molecular sciences*, *20*(6), 1445.
74. Tagawa, M., Kawamura, K., Li, Q., Tada, Y., Hiroshima, K., & Shimada, H. (2011). A possible anticancer agent, type III interferon, activates cell death pathways and produces antitumor effects. *Journal of Immunology Research*, *2011*.
75. Toka, F. N., & Golde, W. T. (2013). Cell mediated innate responses of cattle and swine are diverse during foot-and-mouth disease virus (FMDV) infection: a unique landscape of innate immunity. *Immunology letters*, *152*(2), 135-143.

76. Toka, F. N., Nfon, C. K., Dawson, H., Estes, D. M., & Golde, W. T. (2009). Activation of porcine natural killer cells and lysis of foot-and-mouth disease virus infected cells. *Journal of Interferon and Cytokine Research*, *29*(3), 179-192.
77. Wculek, S. K., Cueto, F. J., Mujal, A. M., Melero, I., Krummel, M. F., & Sancho, D. (2020). Dendritic cells in cancer immunology and immunotherapy. *Nature Reviews Immunology*, *20*(1), 7-24.
78. Wicherska-Pawłowska, K., Wróbel, T., & Rybka, J. (2021). Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) in innate immunity. TLRs, NLRs, and RLRs ligands as immunotherapeutic agents for hematopoietic diseases. *International journal of molecular sciences*, *22*(24), 13397.
79. Woolsey, C. (2018). Post-exposure treatment of marburg virus angola disease in non-human primates using recombinant vesicular stomatitis virus vectors (Doctoral dissertation).
80. Yadav, M. P., Singh, R. K., & Malik, Y. S. (2020). Emerging and transboundary animal viral diseases: Perspectives and preparedness. *Emerging and transboundary animal viruses*, 1-25.
81. Yang, F., Zhu, Z., Cao, W., Liu, H., Wei, T., Zheng, M & Zheng, H. (2020). Genetic determinants of altered virulence of type O foot-and-mouth disease virus. *Journal of Virology*, *94*(7), 10-1128.
82. Yang, M., Xu, W., Bittner, H., Horsington, J., Vosloo, W., Goolia, M & Nfon, C. (2016). Generation of mAbs to foot–and–mouth disease virus serotype A and application in a competitive ELISA for serodiagnosis. *Virology journal*, *13*(1), 1-9.
83. Zhang, F., Zhang, Z., Li, X., Li, J., Lv, J., Ma, Z., & Pan, L. (2021). Immune responses to orally administered recombinant lactococcus lactis expressing multi-epitope proteins targeting M cells of foot-and-mouth disease virus. *Viruses*, *13*(10), 2036.
84. Zhang, X., Ma, W., Yang, F., Yang, Y., Lv, L., Wu, J & He, J. (2023). Epidemiological and Genetic Analysis of Foot-and-Mouth Disease Virus O/ME-SA/Ind-2001 in China between 2017 and 2021. *Transboundary and Emerging Diseases*, *2023*.
85. Zhu, J. J., Stenfeldt, C., Bishop, E. A., Canter, J. A., Eschbaumer, M., Rodriguez, L. L., & Arzt, J. (2022). Inferred Causal Mechanisms of Persistent FMDV Infection in Cattle from Differential Gene Expression in the Nasopharyngeal Mucosa. *Pathogens*, *11*(8), 822.